

## CLINICAL NOTE

**Acute lithium poisoning: epidemiology, clinical characteristics, and treatment**

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Lithium continues to be the treatment of choice for bipolar disorder. Acute lithium poisoning is a potentially serious event. We present a retrospective observational significant study of episodes of acute lithium poisoning during a 52-month period. Poisoning was defined by a blood lithium concentration of 1.5 mEq/L or higher. We analyzed treatment and epidemiologic and clinical characteristics of 70 episodes were identified (incidence density among treated patients, 1.76 per 100 patient-years). The most frequent cause of lithium poisoning was a concurrent medical condition (46%). Most poisonings were mild (74.2%), but neurologic involvement was identified in 40.3%. Electrocardiographic abnormalities were found in 8 cases. Acute renal failure, found in 23 patients (37.1%), was mild in most cases, although 11 patients required hemodialysis. We concluded that acute lithium poisoning is an uncommon complication, but risk needs to be lowered. Patients should be warned to avoid dosage errors and to take special care during concurrent illnesses and while taking other medications.

**Keywords:** Lithium. Acute poisoning. Renal failure. Bipolar disorder.

**Epidemiología, características clínicas y tratamiento de la intoxicación aguda por litio**

El litio sigue siendo el tratamiento de elección en el trastorno bipolar. La intoxicación aguda por litio (IAL) es un cuadro potencialmente grave. Se presenta un estudio observacional aleatorizado, retrospectivo de las IAL observadas durante un periodo de 52 meses. Se definió como IAL cuando se registró una concentración de litio en sangre  $\geq 1,5$  mEq/L. Se analizaron sus características clínicas, epidemiológicas y su tratamiento de 70 episodios de IAL (densidad de incidencia: 1,76 IAL por cada 100 pacientes tratados-año). La causa más frecuente de IAL fue un proceso patológico intercurrente (46%). La mayoría fueron de carácter leve (74,2 %), con sintomatología neurológica en el 40,3%. En 8 IAL hubo alteraciones electrocardiográficas, 23 IAL (37,1%) se asociaron con fracaso renal agudo, la mayoría de carácter leve y 11 precisaron hemodiálisis. Se concluye que la IAL es una complicación infrecuente, pero es necesario disminuir su riesgo advirtiendo al paciente ante la existencia de procesos intercurrentes, errores en la posología o polimedición.

**Palabras clave:** Litio. Intoxicación. Fracaso renal. Trastorno bipolar.

**Introduction**

Lithium continues to be the reference mood stabilizer in bipolar disorder (BD)<sup>1</sup>, a disease that can reach a prevalence of 4.4%<sup>2</sup>. However, the therapeutic range of lithium is narrow, presenting serious adverse effects if its blood concentrations rise, requiring periodic monitoring. Acute lithium poisoning (ALP) is a potentially serious pathology, which can condition neurological, cardiologic, and acute renal failure (ARF) symptoms<sup>3</sup>. Faced with this situation, the clinicians of the emergency department, nephrology and psychiatry need to know both the risk of ALP and its detection and management. The aim of this study is to analyse the characteristics of ALP cases and the actions performed for their treatment.

**Clinical cases**

An observational, retrospective study of ALPs observed between January 1, 2011 and April 30, 2015 (54

months) was carried out at the Ramón y Cajal University Hospital (HURC), which covers a mental health area of 600,000 inhabitants. An ALP case was defined as the concentration of lithium in blood  $\geq 1.5$  mEq/L<sup>4</sup>. ALP cases were identified by reviewing the lithium determinations in the HURC Biochemistry Service database. The ALP was stratified as mild (1.5-2.39 mEq/L), moderate (2.4-3.49 mEq/L) or severe ( $\geq 3.5$  mEq/L)<sup>5</sup>. Once identified, they were individually studied using the medical history of each patient. It was considered ARF to the acute increase in serum creatinine concentration  $\geq$  (Serum creatinine less than twice the baseline), AKIN-2 (greater than twice the baseline) and AKIN-3 (higher than Triple basal). The study was approved by the Clinical Research Ethics Committee of the HURC.

Statistical analysis was used SPSSv20 and quantitative variables were compared in the two groups using Student t and Mann Whitney U, according to the distribution of the variables. For the dichotomous qualitative variables, Fisher's exact test or Pearson's chi square was used, depending on whether the expected frequency was lower than 5 or not, respectively.

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All authors have confirmed their authorship in the author's responsibilities document, publication agreement and assignment of rights to EMERGENCIAS.

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Of a total of 6,069 lithemias corresponding to 917 patients chronically treated with lithium salts [531 women (57.9%) and 386 men (42.1%),  $p < 0.05$ ], 70 episodes of ALP were identified in 62 patients, since some had more than one episode during the period considered. The incidence density was 1.76 episodes of intoxication per 100 patients treated-year. In 8 cases, intoxication was treated and treated in another health area, so they were discarded from the analysis due to lack of clinical information. Finally, the data corresponding to 62 episodes of ALP of 54 patients were analysed (Table 1).

Four main groups of ALP causes were identified: no apparent cause (19.3%), intercurrent process (46.7%), initiation or modifications in the lithium dose (22.5%) and manic phases (11.3 %). In the group of episodes with no apparent cause, the detection of ALP was accidental when a routine determination was made, and no precipitants or previous dose modifications could be detected. All were mild ALPs, without clinical presentation or treatment. Almost half of the ALP episodes were associated with an intercurrent pathologic process and were mild in 19 cases, moderate in 9 and severe in 1. Intravascular volume depletion was observed in 13 episodes (gastrointestinal, diuretic or mixed treatment). Other causes were 7 confusional medical record, 6 infectious processes or 3 exacerbations of other medical surgical pathologies, possibly also associated with a lower hydrosaline intake. Initiation or modification of the lithium dose was seen in 14 episodes of ALP. In 8, they were mild, moderate in 4, and severe in 2. Six episodes were due to a voluntary overdose of suicide attempt. Finally, a manic exacerbation of the disease was subjacent in 7 ALPs, some related to an increase of the dose by the psychiatrist. All of these were mild.

Figure 1 shows the different causes of intoxication according to age and sex. In our cohort, the proportion of women treated with lithium exceeds that of males. The ALP rate was also significantly higher in females (44 episodes, 8.3%) than in males (18 episodes, 4.7%) (Table 1). Age, although higher in men, did not show significant differences with respect to women. In men older than 60 years, the underlying cause of intoxication was an intercurrent pathological process in 77.8%. In contrast, women were at increased risk for ALP after an increase in the prescribed dose or after an attempted suicide.

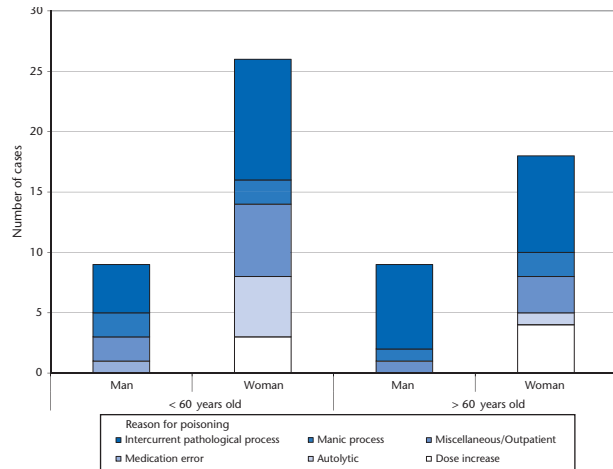


Figure 1. Intoxication motives according to age and sex.

In relation to severity, mild intoxication (74.2%) was the most frequent, followed by moderate (21.0%) and severe (4.8%) intoxication. Neurological impairment was the most frequent clinical alteration (40.3%) in the form of tremor (7 cases), dizziness and instability (6), somnolence or bradypsychia (8), psychomotor agitation (2) or decreased consciousness (2). The presence of neurological symptoms was associated with age and sex: age over 60 had an OR of 3.12 (95% CI: 1.08-8.97) and women had an OR of 0.29 (95% CI: 0.09-0.92). The second clinical manifestation in frequency was ARF (37.1%), mostly mild: 17 AKIN-1, 5 AKIN-2 and 1 AKIN-3. ARF was associated with age [patients over 60 years old: OR 4.21 (95% CI: 1.41-12.6)]. Only 11 cases (17.7%) of ARF required haemodialysis (HD). Finally, 8 cases of moderate or severe intoxication (mean lithemia of 3.09 mEq/L), all women, presented electrocardiographic alterations that returned after standardization of the lithemia: flattening of the isolated T wave (4) or associated with QT segment elongation (4).

In 21 cases (45.6%) of mild intoxications, with an average lithemia of 1.64 mEq/L and absence of neurological symptomatology or ARF, ALP was managed by an adjustment of the prescribed lithium regimen and dietary recommendations regarding the intake of salt in the diet with control of lithemia in the following days. In 24 cases (52.2%), with an average lithemia of 1.90

Table 1. Main characteristics of lithium poisonings. Global data and comparison between men and women

	Global		Women			Significance* (P-value)	Men			
	Total	Mild	Moderate	Severe	Total		Severe	Moderate	Mild	
Number of episodes (n)	62	32	9	3	44	0.003	18	0	4	14
Age (years) [mean (SD)]	56 (13.1)	56.2 (13.3)	51.7 (13.1)	43.3 (6.7)	54.3 (13)	N.S.	57.6 (12)	-	60.2 (13.4)	56.9 (12)
Lithemia in mEq / L [mean (DE)]	2.1 (0.8)	1.8 (0.2)	2.9 (0.4)	4.7 (1.0)	2.2 (0.9)	N.S.	2.0 (0.4)	-	2.7 (0.2)	1.8 (0.2)
Acute renal failure [n (%)]	23 (37)	8 (25)	6 (66)	1 (33)	15 (34)	N.S.	8 (44)	-	3 (75)	5 (36)
Haemodialysis [n (%)]	11 (18)	1 (3)	6 (66)	3 (100)	10 (22)	N.S.	1 (5.5)	-	1 (25)	0 (0)
Neurological [n (%)]	25 (40)	9 (28)	4 (44)	1 (33)	14 (32)	0.035	11 (55)	-	4 (100)	7 (50)
Income [n (%)]	24 (39)	9 (28)	6 (67)	3 (100)	18 (41)	N.S.	6 (33)	-	2 (50)	4 (28)

DE: standard deviation; N.S.: not significant.

\*For comparison of totals between men and women.

mEq/L, the treatment was hydrosaline replacement. All moderate intoxications were treated with supportive measures, including volume expansion with serum therapy and monitoring. Seven patients (53%) required HD for the treatment of intoxication. In all serious poisonings, HD was prescribed. Two of these patients required mechanical ventilation.

## Discussion

In our study, it was observed that ALP had an incidence density of 1.76 cases per 100 treated patients per year, reflecting an incidence and a low risk, especially considering that the majority were mild (74.2%).

Lithium treatment protocols advise the patient about the risks of increasing their concentrations in certain circumstances (diets poor in sodium, pharmacological interaction or dehydration). Our study shows that these were the most frequent causes of intoxication, which reinforces the need to insist on the education of patients in this regard.

In some cases, although mild, the ALP was due to changes in treatment or to the initiation of treatment. These situations also require a dose adjustment in a safe manner, increasing the frequency of the determinations. Other causes of intoxication, such as suicide attempts, are part of other specific prevention programs<sup>7</sup>.

The ALPs were more frequent in women (8.3%) than in men (4.7%), which seems to indicate a greater susceptibility by the female sex. Different triggers linked to a different volume of distribution and a smaller body surface could explain these findings.

As the age increases we observe a higher rate of events initiated after an intercurrent pathological process, and this data is especially striking in the group of males where it reaches 77.8%. They are multifactorial processes, where drug interactions, in a population with greater comorbidity and polypharmacy, coupled with volume depletion will play an important role. Therefore, the precautions mentioned above should be emphasized in the elderly population.

In this series, only 18% of patients required treatment with HD. Its indication leaves no doubt in severe or moderate intoxications with great neurological, cardiologic or renal involvement. The dilemma arises in other ALPs with less affectation. In a recent review of the literature, HD is recommended when it is expected that the period until normalization of lithium may exceed 36 hours<sup>8</sup>.

In conclusion, ALP is an infrequent, although potentially serious and multidisciplinary management complication. Its frequency is higher in women, and different triggers are associated with it. Therefore, it is necessary

to reduce the risk of errors in the dosage, to control the polymerization and to know the intercurrent processes that can precipitate it.

## Conflicting interests

Dr. Montes has received research funding from the Ministry of Health, Social Services and Equality, Lundbeck and Ferrer. Has been in the group of lecturers of Ludbeck, Janssen, Otsuka, Ferrer, Pfizer. The rest of the authors declare no conflict of interest in relation to the present work.

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## Ethical Responsibilities

The study was approved by the Comité de Ética e Investigación Clínica del Hospital Ramón y Cajal.

Informed consent was obtained from participants.

All authors have confirmed the maintenance of confidentiality and respect for patients' rights in the author's responsibilities document, publication agreement and assignment of rights to EMERGENCIAS.

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